POLYCONDENSED HETEROCYCLES. VIII.

SYNTHESIS OF 11-ARYL-5H,11H-PYRROLO[2,1-c][1,4]BENZOTHIAZEPINES BY *PUMMERER REARRANGEMENT-CYCLIZATION REACTION*

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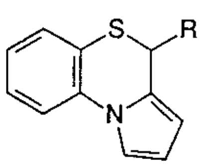
Abstract - 11-Phenyl-5H,11H-pyrrolo[2,1-c][1,4]benzothiazepine has been prepared by an intramolecular nucleophilic displacement reaction. The same compound, as well as some analogues thereof, were more conveniently obtained by Pummerer rearrangement-cyclization of sulfinyl precursors. The latter method was also effective for the synthesis of 4-phenyl-4H-pyrrolo[2,1-c][1,4]benzothiazine.

In 1986 Bates[1] developed a fine procedure to achieve several 4H-pyrrolo[2,1-c][1,4]benzothiazines (1, R = COPh, CN, COOEt) starting from sulfoxide precursors by an intramolecular capture of Pummerer rearrangement intermediates, conducted in refluxing toluene containing two equivalents of trifluoroacetic acid. During our previous searches, we confirmed the effectiveness of this method in obtaining 5H,11H-pyrrolo[2,1-c][1,4]benzothiazepines (2, R = CN, COOEt), too.[2] In both cases, it proved impossible to prepare compounds lacking an electron withdrawing group on the α-carbon to the sulfur: in fact, such treatment was unsuccessful when applied to "unactivated" sulfoxides,



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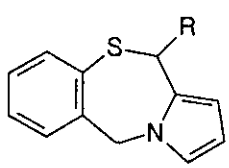

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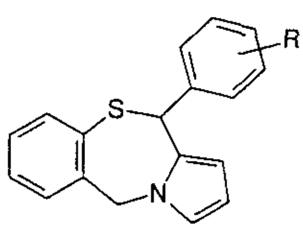


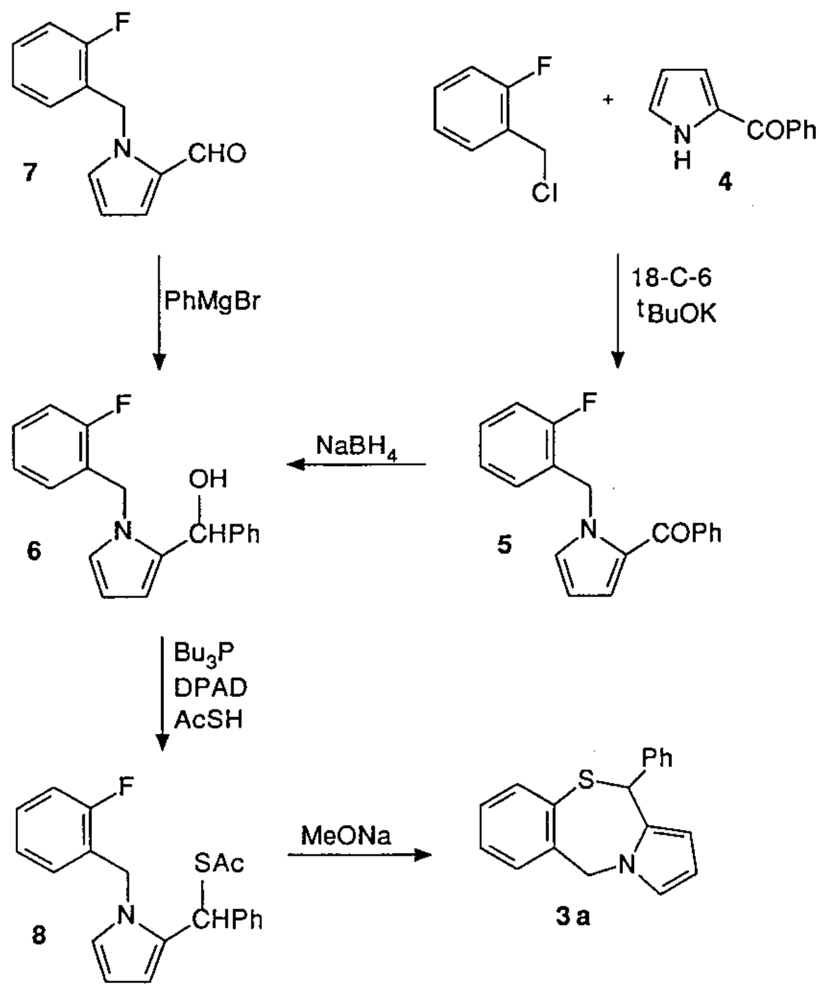
3

because they led to complex mixtures or didn't react at all.

For such a reason we prepared 4-(un)substituted 4H-pyrrolo[2,1-c][1,4]benzothiazines (1, R = H, CH_3, CH_2Ph, Ph) as well as 5H,11H-pyrrolo[2,1-c][1,4]benzothiazepine (2, R = H) by a sequence involving an intramolecular nucleophilic aromatic fluoride displacement-cyclization as a key step.[2,3]

Afterwards, in connection with a program related to the development of certain Ca-blockers and non-steroidal antiinflammatory agents, we needed 11-aryl-5H,11H-pyrrolo[2,1-c][1,4]benzothiazepines (3). Accordingly, we planned to synthesize our target compounds (3) following the latter procedure as outlined in Scheme 1. N-Alkylation of 2-benzoylpyrrole (4)[4] with 2-fluorobenzyl chloride,

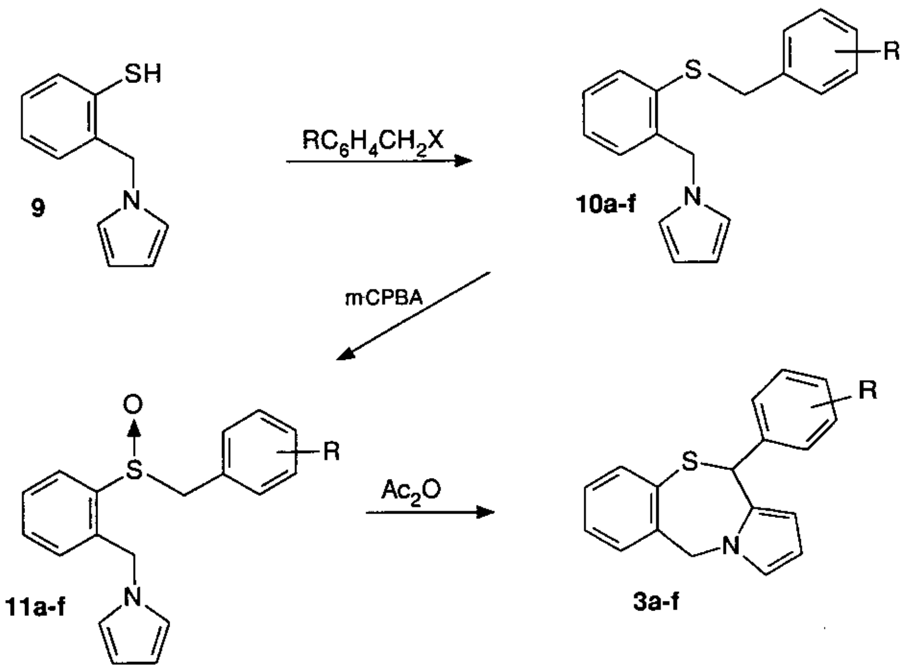
Scheme 1



followed by sodium borohydride reduction, afforded the alcohol (6), which was also prepared by addition of phenylmagnesium bromide to 1-(2-fluorobenzyl)pyrrolo-2-carbaldehyde (7).[2] Modified Mitsunobu reaction of 6 with thiolacetic acid gave 1-(2-fluorobenzyl)-2-[(α-acetylthio)benzyl]pyrrole (8), which was directly cyclized by means of sodium methoxide in N,N-dimethylformamide as a solvent to furnish 3a in satisfactory overall yield. However, the demanding procedure and the troublesome purification of the sensitive intermediates suggested undertaking an alternative route.

Thus we decided to reinvestigate the one-pot Pummerer-cyclization reaction of sulfoxides (11), easily available from the corresponding sulfides (10), and we were delighted to find that a smooth conversion of 11 to 11-aryl-5H,11H-pyrrolo[2,1-c][1,4]benzothiazepines (3) could be achieved in acceptable to good yield on simply refluxing with acetic anhydride (Scheme 2).

Scheme 2

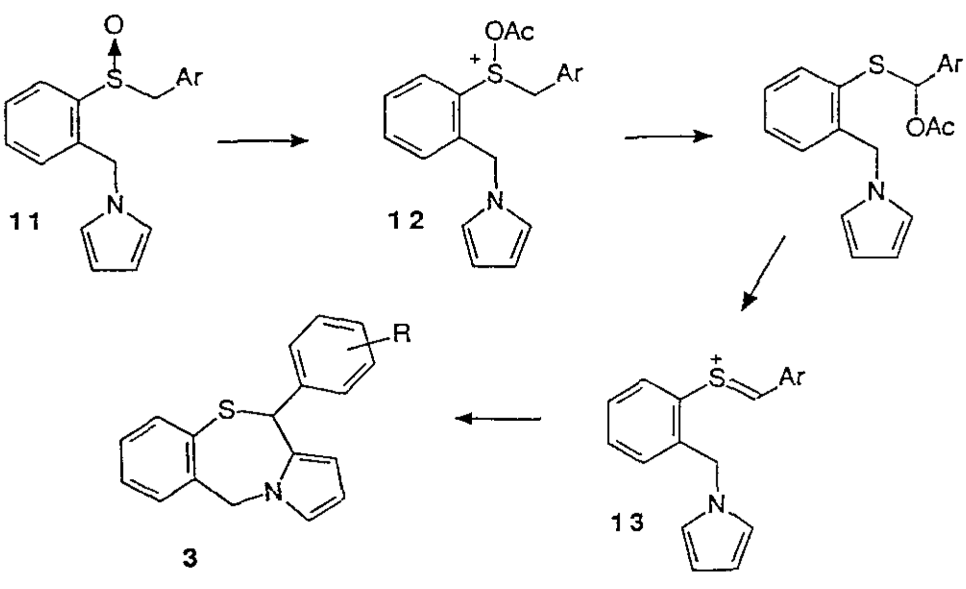


R = (a) H, (b) 4-Me, (c) 4-F, (d) 4-Cl, (e) 2-F, (f) 4-NO_2

Furthermore, also 4-phenyl-4H-pyrrolo[2,1-c][1,4]benzothiazine (1, R = Ph), previously prepared by a different procedure,[3] was obtained in 70% yield when 1-(2-benzylsulfinylphenyl)pyrrole[1] was similarly treated with acetic anhydride.

The mechanism we propose for this process, shown in Scheme 3, involves formation of the thionium ion (13) from an acetilated sulfoxide (12) followed by intramolecular cyclization to 3. The presence on the α-carbon to the sulfoxide of an aryl group, wich strongly stabilizes the ion (13), is an essential requirement for the success of the reaction. On the contrary, electron withdrawing groups are detrimental for this process since they prevent the formation of 13. Hence our procedure proved to be complementary to the Bates' method.[1]

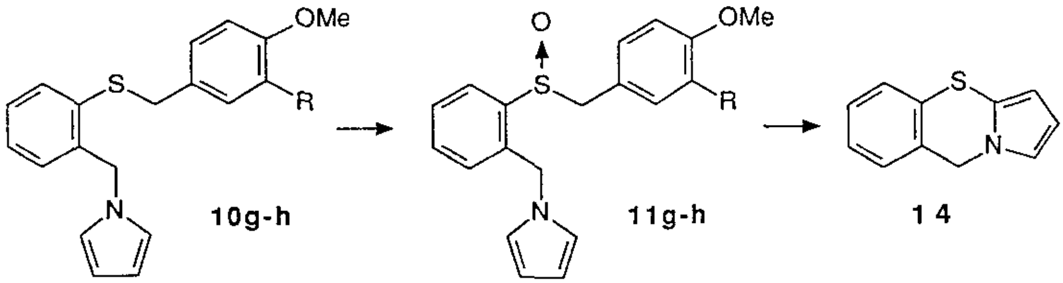
Scheme 3



The addition of either sodium acetate[5] or PTSA[6] did not improve the course of the reaction. On the other hand, substitution of acetic anhydride with the more electrophilic trifluoroacetic anhydride,[7] in order to employ milder conditions (lower temperature, shorter reaction time), was precluded on account of the reactivity of the pyrrole ring towards this reagent.

Amongst the studied sulfoxides, only the methoxy substituted derivatives (11g) and (11h) did not succeed in producing the expected tricyclic compounds, the sole isolated product being in both cases the unknown 9H-pyrrolo[2,1-b][1,3]benzothiazine (14) (Scheme 4).[8]

Scheme 4



R = (g) H, (h) OMe

EXPERIMENTAL

Melting points were taken on an Electrothermal 8103 apparatus and are uncorrected. Ir spectra (neat or nujol mulls) were taken on a Perkin-Elmer 398 spectrophotometer: all sulfoxide derivatives showed a band at 1030-1060 cm^{-1} (SO). Mass spectra were recorded on a VG 70/250S spectrometer with an electron beam of 70 eV. ^{1}H-Nmr spectra were recorded on a Varian XL 200 spectrometer for $CDCl_3$ solution: the values of chemical shifts (δ) are expressed in ppm and coupling constants (J) in Hz. Chromatographic purifications were performed on columns packed with Merck silica gel 60, 230-400 mesh, by flash technique. Microanalyses were performed on a Perkin-Elmer 240 C elemental analyzer. Anhydrous sodium sulfate was utilized to dry organic extracts. All the reactions were carried out under a nitrogen atmosphere.

1-(2-Fluorobenzyl)-2-benzoylpyrrole (5).

To a stirred solution of potassium t-butoxide (3.36 g, 30 mmol) and 18-crown-6 (0.79 g, 3 mmol) in anhydrous THF (60 ml), 2-benzoylpyrrole[4] (5.13 g, 30 mmol) in the same amount of the same solvent was added dropwise. After 30 min a solution of 2-fluorobenzyl chloride (3.58 ml, 30 mmol) in anhydrous THF (60 ml) was dropped slowly. After stirring overnight, the solvent was evaporated at reduced pressure and the resulting residue was partitioned between ether and water. After an usual work-up, the oily residue was chromatographed on a silica gel column eluting with dichloromethane-petroleum ether (1:1) to obtain 5 (7.62 g, 91%) as a waxy solid of no sharp mp. Ir (nujol): 1630 cm^{-1}. ^{1}H-Nmr: 5.75 (s, 2H), 6.22 (m, 1H), 6.79 (m, 2H), 7.01-7.82 (m, 9H). Anal. Calcd for $C_{18}H_{14}NOF$: C,77.40; H,5.05; N,5.01. Found: C,77.21; H,4.96; N,4.80.

1-(2-Fluorobenzyl)-2-(α-hydroxybenzyl)pyrrole (6).

Starting from 5.

A solution of 5 (5.02 g, 18 mmol) in 2-propanol (30 ml) was added dropwise to a stirred suspension of sodium borohydride (1.37 g, 36 mmol) in the same solvent (30 ml). The mixture was stirred at 80°C for 18 h. Removal of the 2-propanol gave a white semi-solid which was stirred with water for 15 min, then extracted with dichloromethane. The organic layer was washed with water until neutrality, then dried. After evaporation, pure 6 (4.9 g, 97%) was obtained as a white solid. mp: 108-109°C (cyclohexane). Ir (nujol): 3170 cm^{-1}. ^{1}H-Nmr: 2.13 (d, J=5.1, 1H, exchangeable), 5.10 (half of AB q, J=16.4, 1H), 5.33 (half of AB q, J=16.4, 1H), 5.83 (d, J=5.1, 1H), 5.86 (m, 1H), 6.10 (t, J=3.2, 1H), 6.67-7.38 (m, 10H). Anal. Calcd for $C_{18}H_{16}NOF$: C,76.85; H,5.73; N,4.98. Found: C,76.70; H,5.83; N,4.85.

Starting from 7.

1-(2-Fluorobenzyl)pyrrolo-2-carbaldehyde (7) (1.62 g, 8 mmol) in anhydrous THF (25 ml) was added dropwise to a 3M ethereal solution of phenylmagnesium bromide (8 ml, 24 mmol). The mixture was gently warmed for 4 h, then cooled and quenched in cold aqueous saturated ammonium chloride. After extractive work-up with dichloromethane, 6 was obtained as a solid which was recrystallized from cyclohexane (1.9 g, 85%).

1-(2-Fluorobenzyl)-2-[(α-acetylthio)benzyl]pyrrole (8).

To a well stirred and cooled (0°C) solution of tributylphosphine (1.41 g, 7 mmol) in anhydrous THF (5 ml), diisopropyl azodicarboxylate (DPAD) (1.41 g, 7 mmol) was added dropwise. After 30 min a solution of 6 (1.0 g, 3.5 mmol) and thiolacetic acid (0.5 ml, 7 mmol) in anhydrous THF (5 ml) was added slowly. The mixture was stirred for 1 h at 0°C, then for 2 days at room temperature. Removal of the solvent left a residue which was chromatographed with 0→2% ether in hexanes to afford 8

(1.0 g, 83%) as a pale yellow oil. Ir (neat): 1690 cm^{-1}. ^{1}H-Nmr: 2.27 (s, 3H), 5.01 (half of AB q, J=16.7, 1H), 5.15 (half of AB q, J=16.7, 1H), 5.84 (s, 1H), 6.13 (m, 1H), 6.70 (m, 1H), 6.89-7.38 (m, 10H).

11-Phenyl-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine (3a).

8 (0.78 g, 2.3 mmol) was dissolved in freshly distilled *N,N*-dimethylformamide (6 ml) and cooled to -20°C. Sodium methoxide (0.32 g, 5.9 mmol) was added portionwise. The mixture was stirred at -20°C for 1 h, then at room temperature for 3 h. Neutralization (acetic acid) and evaporation *in vacuo* of the volatiles afforded a residue, which was taken up in ether. The resulting solution was washed with water and dried. After removal of the solvent, a solid was obtained and recrystallized from cyclohexane to afford 3a (0.45 g, 70%) as nearly white crystals.

General procedure for the preparation of 10a-h and 11a-h.

The general methods were formerly described in our previous papers.[2,9]
Physical and spectral data of new compounds are listed in Tables 1 and 2.

General procedure for the preparation of 3a-f and 1 (R = Ph).

A mixture of the appropriate sulfoxide (11a-f) or 1-(2-benzylsulfinylphenyl)pyrrole[1] (1 mmol) and acetic anhydride (25 ml) was refluxed for the required time (5-8 h). After cooling, the solution was treated with aqueous saturated sodium carbonate, then extracted with ether. Drying and evaporation gave essentially pure 3a-f or 1(R=Ph), which was recrystallized [in some instances a preliminary purification by column chromatography, using benzene-cyclohexane (1:5) as an eluent, was advisable].
In the case of 11g and 11h, this procedure led to 14 in 27% and 32% yield respectively.
Physical and spectral data of tricyclic compounds are listed in Tables 1 and 3.

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Table 1. Physical and chemical data for new compounds

Compd	mp (°C)	Cryst. solvent	Yield %	Formula	Elemental Analysis Calcd/Found		
					C	H	N
10b	74–75	petroleum ether	85	$C_{19}H_{19}NS$	77.77/77.77	6.53/6.77	4.77/4.83
10c	52	petroleum ether	94	$C_{18}H_{16}NFS$	72.70/72.72	5.42/5.45	4.71/4.46
10d	54	petroleum ether	88	$C_{18}H_{16}NClS$	68.89/68.98	5.14/5.39	4.46/4.42
10e	43	petroleum ether	86	$C_{18}H_{16}NFS$	72.70/72.64	5.42/5.51	4.71/4.46
10g	83–84	cyclohexane	86	$C_{19}H_{19}NOS$	73.75/73.45	6.19/5.92	4.53/4.25
10h	77–78	cyclohexane	79	$C_{20}H_{21}NO_2S$	70.76/70.99	6.24/6.45	4.13/3.90
11a	158	ethanol	94	$C_{18}H_{17}NOS$	73.19/73.13	5.80/5.88	4.74/4.68
11b	178–179	ethanol	90	$C_{19}H_{19}NOS$	73.75/74.01	6.19/6.41	4.53/4.47
11c	149	ethanol	84	$C_{18}H_{16}NOFS$	68.98/69.03	5.15/5.18	4.47/4.29
11d	165–167	ethanol	89	$C_{18}H_{16}NOClS$	65.54/65.72	4.89/4.84	4.25/3.99
11e	146	ethanol	82	$C_{18}H_{16}NOFS$	68.98/69.19	5.15/5.10	4.47/4.44
11g	158–159	ethanol	94	$C_{19}H_{19}NO_2S$	70.12/70.24	5.88/5.99	4.30/4.27
11h	133–134	ethanol	78	$C_{20}H_{21}NO_3S$	67.58/67.32	5.95/6.28	3.94/3.94
3a	127–128	cyclohexane	73	$C_{18}H_{15}NS$	77.94/78.19	5.45/5.51	5.05/5.06
3b	150–151	cyclohexane	67	$C_{19}H_{17}NS$	78.31/78.55	5.88/5.90	4.81/4.62
3c	106	cyclohexane	49	$C_{18}H_{14}NFS$	73.19/73.40	4.78/4.90	4.74/4.54
3d	149	cyclohexane	66	$C_{18}H_{14}NClS$	69.33/69.41	4.52/4.59	4.49/4.37
3e	undet.	cyclohexane	40	$C_{18}H_{14}NFS$	73.19/72.96	4.78/4.74	4.74/4.60
3f	148–149	cyclohexane	42	$C_{18}H_{14}N_2O_2S$	67.06/67.33	4.38/4.38	8.69/8.59
14	93	petroleum ether	a	$C_{11}H_9NS$	70.55/70.22	4.84/4.91	7.48/7.26
1 (R=Ph)	117–118	cyclohexane	70	$C_{17}H_{13}NS$	77.52/77.67	4.97/4.89	5.31/5.29

[a] See experimental

Table 2. Partial ^{1}H-Nmr spectral data for new sulfide and sulfinyl compounds

Compd	δ (ppm)
10b	2.32 (s, 3H), 3.97 (s, 2H), 4.97 (s, 2H), 6.16 (m, 2H), 6.55 (m, 2H)
10c	3.93 (s, 2H), 5.03 (s, 2H), 6.17 (t, J=2.0, 2H), 6.59 (t, J=2.0, 2H)
10d	3.91 (s, 2H), 5.01 (s, 2H), 6.17 (t, J=2.1, 2H), 6.58 (t, J=2.1, 2H)
10e	4.02 (s, 2H), 5.04 (s, 2H), 6.18 (t, J=2.1, 2H), 6.59 (t, J=2.1, 2H)
10g	3.79 (s, 3H), 3.96 (s, 2H), 5.01 (s, 2H), 6.17 (t, J=2.1, 2H), 6.59 (t, J=2.1, 2H)
10h	3.76 (s, 3H), 3.86 (s, 3H), 3.93 (s, 2H), 5.00 (s, 2H), 6.16 (t, J=2.0, 2H), 6.58 (t, J=2.0, 2H)
11a	3.52 (s, 2H), 4.61 (half of AB q, J=15.3, 1H), 4.92 (half of AB q, J=15.3, 1H), 6.17 (t, J=2.1, 2H), 6.52 (t, J=2.1, 2H)
11b	2.33 (s, 3H), 3.50 (half of AB q, J=12.5, 1H), 3.63 (half of AB q, J=12.5, 1H), 4.49 (half of AB q, J=15.6, 1H), 4.90 (half of AB q, J=15.6, 1H), 6.17 (t, J=2.1, 2H), 6.49 (t, J=2.1, 2H)
11c	3.10 (half of AB q, J=12.9, 1H), 3.39 (half of AB q, J=12.9, 1H), 4.99 (s, 2H), 6.20 (m, 2H), 6.60 (m, 2H)
11d	3.09 (half of AB q, J=12.7, 1H), 3.37 (half of AB q, J=12.7, 1H), 5.01 (s, 2H), 6.19 (t, J=2.1, 2H), 6.59 (t, J=2.1, 2H)
11e	3.71 (q, J=11.0, 2H), 4.76 (half of AB q, J=15.4, 1H), 5.07 (half of AB q, J=15.4, 1H), 6.18 (t, J=2.1, 2H), 6.57 (t, J=2.1, 2H)
11g	3.46 (s, 2H), 3.79 (s, 3H), 4.65 (half of AB q, J=15.2, 1H), 4.94 (half of AB q, J=15.2, 1H), 6.18 t, J=2.1, 2H), 6.53 (t, J=2.1, 2H)
11h	3.44 (s, 2H), 3.68 (s, 3H), 3.86 (s, 3H), 4.68 (half of AB q, J=15.1, 1H), 4.95 (half of AB q, J=15.1, 1H), 6.18 (t, J=2.1, 2H), 6.54 (t, J=2.1, 2H)

Table 3. ^{1}H-Nmr and ms spectral data for tricyclic compounds

Compd	δ (ppm)	ms m/z (%)
3a	5.13 (half of AB q, J=14.4, 1H), 5.39 (half of AB q, J=14.4, 1H), 5.66 (m, 1H), 5.82 (s, 1H), 6.03 (m, 1H), 6.71 (m, 1H), 7.12-7.34 (m, 9H)	277 (M^+, 69)
3b	2.34 (s, 3H), 5.12 (half of AB q, J=14.4, 1H), 5.37 (half of AB q, J=14.4, 1H), 5.64 (m, 1H), 5.80 (s, 1H), 6.01 (m, 1H), 6.70 (m, 1H), 7.11-7.31 (m, 8H)	291 (M^+, 73)
3c	5.10 (half of AB q, J=14.3, 1H), 5.40 (half of AB q, J=14.3, 1H), 5.62 (m, 1H), 5.77 (s, 1H), 6.02 (m, 1H), 6.71 (m, 1H), 6.93-7.01 (m, 2H), 7.14-7.36 (m, 6H)	295 (M^+, 56)
3d	5.10 (half of AB q, J=14.4, 1H), 5.39 (half of AB q, J=14.4, 1H), 5.63 (m, 1H), 5.72 (s, 1H), 6.02 (m, 1H), 6.71 (m, 1H), 7.14-7.34 (m, 8H)	311 (M^+, 58)
3e	5.17 (half of AB q, J=14.2, 1H), 5.53 (half of AB q, J=14.2, 1H), 5.68 (m, 1H), 6.06 (m, 1H), 6.14 (s, 1H), 6.74 (m, 1H), 6.94-7.39 (m, 8H)	295 (M^+, 54)
3f	5.10 (half of AB q, J=14.0, 1H), 5.51 (half of AB q, J=14.0, 1H), 5.66 (m, 1H), 5.71 (s, 1H), 6.05 (m, 1H), 6.73 (m, 1H), 7.13-7.40 (m, 6H), 8.05 (d, J=8.8, 2H)	322 (M^+, 26)
14	4.97 (s, 2H), 6.17 (m, 2H), 6.83 (m, 1H), 7.21-7.39 (m, 4H)	187 (M^+, 97)
1 (R=Ph)	5.33 (s, 1H), 5.76 (m, 1H), 6.31 (t, J=3.2, 1H), 7.07 (m, 1H), 7.17-7.52 (m, 9H)	263 (M^+, 47)

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